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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,823	06/25/2003	Olivier De Lacharriere	016800-515	1993

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EXAMINER

BALLARD, KIMBERLY

ART UNIT	PAPER NUMBER
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1649

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/602,823	Applicant(s) LACHARRIERE ET AL.	
	Examiner Kimberly Ballard	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 February 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37-54 and 64-95 is/are pending in the application.
- 4a) Of the above claim(s) 39,40,45,46 and 64-67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37,38,41-44,47-54 and 68-95 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on November 13, 2009 and February 18, 2010 have been entered.

Status of Application, Amendments, and/or Claims

2. Claims 37, 53, 68, 70, 78, 87 and 92 have been amended as requested in the amendment filed July 14, 2009. Following the amendment, claims 37-54 and 64-95 are pending in the instant application.

3. Claims 39, 40, 45, 46, and 64-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 17, 2006.

4. Claims **37, 38, 41-44, 47-54, and 68-95** are under examination in the current office action.

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5. Applicant's arguments with respect to claims 37, 38, 41-44, 47-54 and 68-95 have been considered but are moot in view of the new ground(s) of rejection discussed below.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 37, 38, 41-44, 47-54, 68-80 and 82-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,241,993 B1 to Breton et al. (issued June 5, 2001) in view of Robinson & Perkins (*Contact Dermatitis*, 2001; 45:205-213, cited previously), and Trevisani et al. (*Nat Neurosci.* 2002 Jun; 5(6):546-551; e-publication date: 05/07/2002).

Claims 37 and 53 (and dependent claims thereof) are directed to a non-therapeutic method of identifying persons having sensitive skin to a capsaicinoid by application of an aqueous or non-aqueous alcoholic solution comprising a stimulant, a capsaicinoid or capsaicin at a concentration of between $1 \times 10^{-6}\%$ and $5 \times 10^{-4}\%$ comprising a physiologically acceptable aqueous alcohol vehicle to a skin area, and deducing information regarding the skin reactivity as a function of the unattractive sensations. Claims 68-80 and 82-95 are drawn to a non-therapeutic method of evaluating the level of skin neurosensitivity of an adult individual to a capsaicinoid, comprising applying to a skin area of the individual a composition comprising an aqueous or aqueous-alcoholic solution and a capsaicinoid at a concentration of between $1 \times 10^{-6}\%$ and $5 \times 10^{-4}\%$ by weight, recording whether the individual detects or perceives an unattractive sensation, and deducing therefrom information regarding the skin neurosensitivity of the individual. Additional claim limitations recite additional method steps, stimulant concentrations or concentration gradient increases, skin areas

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for testing, ethanol percentages, and waiting times between application and assessment.

Breton et al. disclose a method for determining whether or not an individual has sensitive skin. Breton notes that there is a nexus between individuals with sensitive skin and those who react to a topical application of capsaicin (see column 2, lines 43-48). In particular, the capsaicin test entails applying to a small area of skin 0.05 ml of a cream containing 0.075% capsaicin and in noting the appearance of subjective signs induced by this application, such as stinging, burning and itching. Breton teaches that in individuals having sensitive skin, these signs appear between 3 and 20 minutes after application (see column 2, lines 49-54).

Breton also notes that capsaicin induces a release of neuropeptides from sensitive nerve fibers, such as in sensitive skin, and include tachykinins, CGRP, and Substance P (see paragraph spanning columns 2-3).

The difference between the teachings of Breton and the instant invention is that the prior art document by Breton does not teach that the capsaicin is in an aqueous or aqueous-alcoholic solution, that the concentration of the capsaicinoid is between $1 \times 10^{-6}\%$ and $5 \times 10^{-4}\%$, the specific skin area to be tested, that the concentration of the capsaicinoid is increased until the individual detects the stimulant (i.e., capsaicin), or that the aqueous-ethanolic solution contains a certain percentage of ethanol in water.

Robinson et al. teach a method of assessing skin irritation by using 100-10,000 mM capsaicin in 80% ethanol dried onto filter papers, then rehydrated with water and applied onto the forearm of the subjects, and waiting 3 minutes (i.e., 180 seconds)

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before recording the sensory responses for both treatment and control skin areas (the opposite arm exposed to vehicle served as non-treated control) (see “Materials and Methods” pp. 206-207). The sensory responses perceived by the subjects and used to assess the treatment included stinging, burning, pruritis or itching, hotness, or pins and needles (see pp. 206-207). Robinson et al. further teach that the concentration of capsaicin was increased by a factor between 1 and 10 and application of capsaicin was repeated until a moderate sensory response was elicited, at which concentration no further exposures were performed (see Figure 5, p. 210).

Trevisani et al. teach that ethanol on its own (0.1-3%) can elicit a concentration-dependent release of Substance-P-like immunoreactivity (SP-LI) in various tissues, including skin (see Figure 1e, p. 547). Trevisani notes that the concentrations of ethanol used in the studies were lower than most alcoholic beverages or medications, which can be up to 30% ethanol (see p. 549, 2nd column). Additionally, Trevisani demonstrates that ethanol can potentiate the effects of capsaicin at vanilloid receptor-1 (VR-1), such as the enhancement of calcium response to capsaicin (see Figure 2, p. 548). For example, the presence of ethanol (0.1-1%) dose-dependently enhanced the calcium response of hVR-1 expressing HEK293 cells to capsaicin (0.1 nM to 10 μ M) (see Figure 2f). And 3% ethanol was capable of potentiating VR1 inward currents responsive to 500 nM capsaicin (see Figure 3). It is noted that capsaicin concentrations disclosed by Trevisani fall within and/or encompass the instantly recited capsaicin concentration range of $1 \times 10^{-6}\%$ and $5 \times 10^{-4}\%$ by weight. For example, 0.1 nM to 10

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μM capsaicin would be equivalent to approximately $3.12 \times 10^{-9}\%$ to $3.12 \times 10^{-4}\%$ by weight.

Based upon the teachings of Breton et al., the ordinary-skilled artisan would have recognized that individuals having sensitive skin could be identified by skin sensitivity testing to capsaicin application to the skin. The artisan would have also been aware of the teachings of Robinson et al., who disclose procedures for evaluating self-perceived skin reactivity to various stimuli, including capsaicin in an ethanol solution. And based upon the teachings of Trevisani et al., the artisan would have recognized that ethanol can potentiate capsaicin-induced responses at VR1 (the receptor that mediates capsaicin effects).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was filed to modify the method of identifying individuals having sensitive skin, as taught by Breton et al., according to the teachings of Robinson et al. and Trevisani et al. to arrive at the claimed invention. In particular, the skilled artisan would have recognized that ethanol alone can elicit skin responses at the VR1 receptor similar to those of capsaicin, and can potentiate the effects of capsaicin. Because the results of the capsaicin studies in Robinson et al. demonstrate that even at the lowest capsaicin concentration used there was still a "moderate" response by the subjects (who were representative of "normal" skin types and not necessarily "sensitive skin" types), the artisan would have recognized that lower concentrations of capsaicin would be necessary to identify "sensitive" skin individuals, such as by the subjects' perception of low threshold concentrations of capsaicin. Additionally, the artisan would have been

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motivated to use a lower concentration of capsaicin and/or ethanol based upon the teachings of Trevisani, who demonstrate a potentiating effect of ethanol on capsaicin-mediated VR1 responses, such as in the skin. The artisan would have a reasonable expectation that such a modified method could be successfully used to identify individuals having sensitive skin and/or to evaluate skin neurosensitivity based upon the reported use of such a method by Breton, and based upon the demonstrated results of Robinson.

Moreover, a particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the concentrations of capsaicin and ethanol are clearly recognized result-effective variables that a person of ordinary skill in the art would routinely optimize (see MPEP § 2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal concentration of capsaicin and/or ethanol to be used in the screening method. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of concentrations would have been obvious at the time of Applicants' invention.

Response to Arguments

8. With respect to the teachings of Robinson et al. based upon the previous rejection under 35 U.S.C. 103, in the response filed February 18, 2010, Applicants

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argue that by using the method according to the presently claimed method, i.e., by using low capsaicin concentrations of between $1 \times 10^{-6}\%$ and $5 \times 10^{-4}\%$, the post-filing art by Applicants (Jourdain et al. *J Cosmet Sci*, 2005; 56:153-166) was able to divide the population into at least two groups (pertaining to skin neurosensitivity), which allegedly was not so easy to do with prior-art tests. Applicants assert that the presently claimed methods provide for easier discrimination of individuals according to their neurosensitivity than the method of Robinson et al. Applicants also argue that the criticality of the particular range of concentrations in the presently claimed invention was capable of achieving unexpected results in that claimed method "allows exploring a larger aspect of self-declared sensitive skin" (such as reactivity to environment) than prior-art methods. Additionally, Applicants argue that the lowest concentrations disclosed in Robinson et al. are far from the highest concentration of the range in the presently claimed invention, and therefore one skilled in the art would have had a high probability to choose either a range of capsaicin concentrations either too high or too low and not reach the detection thresholds in the individuals. Finally, Applicants argue that there is nothing in Robinson to suggest that the capsaicin detection thresholds, which allow a gradation of individuals according to their skin sensitivity, would be reached by specifically using the range of concentrations presently claimed, Nor is there any teaching in Robinson to motivate the skilled artisan to improve the accuracy of the method of evaluating skin neurosensitivity by decreasing the irritant concentrations.

9. Applicants' arguments filed February 18, 2010 have been fully considered but are not persuasive. Contrary to Applicants' assertions, the results achieved by the presently

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claimed method, and in particular the criticality of the presently claimed capsaicin range, were hardly unexpected based upon the prior art. As disclosed by Breton et al., identification of individuals having sensitive skin can be performed using a higher concentration of capsaicin. The fact that the concentration range used in the present method (and by Jourdain et al.) allegedly allows for "easier" division of individuals according to skin neurosensitivity compared to the methods of Robinson does not equate to unexpected or surprising results, particularly since the main measure of neurosensitivity in each of the methods is subjective (self-perceived sensitivity), so substantial variation is to be expected. In other words, the differences in observed results between Jourdain et al. (Figure 2) and Robinson et al. (e.g., Figure 7), is not so great as to declare them unexpected. In Robinson's Figure 7, there is still a recognizable division between individuals who are more sensitive to capsaicin and those who are less sensitive to capsaicin. Robinson's method could therefore still be used consistent with claimed invention, i.e., to identify individuals having sensitive skin and/or to evaluate the level of skin neurosensitivity in an individual.

In response to applicant's argument that there is no teaching, suggestion, or motivation to decrease the concentration of capsaicin, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.

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1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Trevisani et al. demonstrate that the ethanol can potentiate the nociceptive responses of VR1 to capsaicin. Therefore, the skilled artisan would reasonably conclude that a lower concentration of capsaicin would be necessary to elicit a threshold detection response in a capsaicin test sample containing ethanol than in a non-ethanol containing sample. Particularly for the identification of individuals having sensitive skin, the ordinary skilled artisan would be motivated to determine the lowest detectable range of capsaicin concentrations in order to better differentiate individuals having "sensitive" skin from those having "normal" skin. Therefore, the combined teachings of the above references render obvious the present invention of claims 37, 38, 41-44, 47-54, 68-80 and 82-95.

10. Claim 81 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,241,993 B1 to Breton et al. (issued June 5, 2001) in view of Robinson & Perkins (*Contact Dermatitis*, 2001; 45:205-213, cited previously), and Trevisani et al. (*Nat Neurosci.* 2002 Jun; 5(6):546-551; e-publication date: 05/07/2002) as applied to claims 37, 38, 41-44, 47-54, 68-80 and 82-95 above, and further in view of Seidenari et al. (*Contact Dermatitis*, 1998; 38(6):311-315, abstract only; cited previously).

The teachings of the combined references are discussed above. While Robinson et al. teaches the application of stimulant to the forearm and cheek for assessment of skin sensitivity, none of the references explicitly teach application to the wing of the nose as recited in instant claim 81.

Seidenari et al. note that the stinging test, which is widely accepted as a marker of sensitivity and employed for the selection of subjects having sensitive skin, is performed by applying an irritant to the nasolabial fold (i.e., the wing of the nose) and evaluating the intensity of subjective symptoms (see abstract).

Thus, it would have been obvious to one of skill in the art at the time the invention was filed to modify the skin sensitivity assessment method taught by Breton, Robinson, and Trevisani by applying the stimulant/irritant (in this case, capsaicin) to the nasolabial fold of the individual being tested. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to substitution of known equivalent elements, i.e. skin area for another, to yield predictable results.

Response to Arguments

11. In the response filed February 18, 2010, Applicants argue that the stinging test is disclosed as lacking objectivity which is a very important criteria to grade individuals in well defined groups. Therefore, Applicants assert, there skilled artisan would have had no apparent reason to combine Seidenari et al. with Robinson et al.

12. Applicants' arguments have been fully considered but are not persuasive. The Seidenari reference was presented merely to evidence that along with the forearm and cheek, the nasolabial fold (wing of the nose) is an art-acknowledged skin area commonly used for sensitivity testing. The ordinary skilled artisan would therefore have recognized that the wing of the nose could also be used for assessment of capsaicinoid

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sensitivity according to the presently recited method. Thus, the combination of references render obvious instant claim 81.

Conclusion

13. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard
Art Unit 1649

/Elizabeth C. Kemmerer/
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